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Dated 16 August 2000

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GB9918962.3.

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

CEREBRUS PHARMACEUTICALS LIMITED,
Incorporated in the United Kingdom,
Oakdene Court,
613 Reading Road,
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United Kingdom

[ADP No. 07745409001]

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THE PATENT OFFICE
11 AUG 1999
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1/77

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Cardiff Road
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1. Your reference — **P022524GB**

2. Patent application number *(The Patent Office will fill in this part)* — **9918962.3** — 11 AUG 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CEREBRUS LIMITED
OAKDENE COURT
613 READING ROAD
WINNERSH
WOKINGHAM
RG41 5UA

SECTION 30(1) (1977 ACT) APPLICATION FILED 27-8-99.

Patents ADP number *(if you know it)* — 7035181002

If the applicant is a corporate body, give the country/state of its incorporation — **UNITED KINGDOM**

4. Title of the invention — **CHEMICAL COMPOUNDS XXII**

5. Name of your agent *(if you have one)* — **Carpmaels & Ransford**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
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WC1A 2RA

Patents ADP number *(if you know it)* — **83001**

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Request for preliminary examination and search *(Patents Form 9/77)*	
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Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford — **Carpmaels & Ransford**

Date: **11th August 1999**

12. Name and daytime telephone number of person to contact in the United Kingdom: **PAUL N. HOWARD** **0171 242 8692**

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CHEMICAL COMPOUNDS XXII

The present invention relates to indole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, *Scrip Reports*, *PJB Publications Ltd*, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

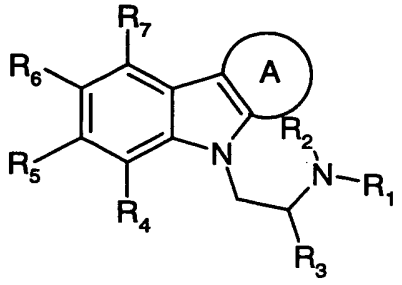
The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **98**, 93-100; G.A. Kennet, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-453) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single injection of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **113**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. Substituted 1,2,3,4-Tetrahydrocarbazoles have been reported as synthetic trypanocides in *J. Med. Chem.*, 1970, **13**, 327 and *J. Med. Chem.*, 1973, **16**, 1411. 9-(2-Dialkylaminopropyl)-1,2,3,4-tetrahydrocarbazoles have been disclosed in

US 2687414 and US 2541211. 7-Substituted-9-(2-dialkylaminoethyl)-1,2,3,4-tetrahydrocarbazoles have been disclosed in DE 930988. The pharmacological behaviour of 2,3-polymethyleneindoles has been described in *J. Med. Chem.*, 1964, **69**, 2910. Derivatives of polynuclear indoles have been described as antidepressants in *J. Med. Chem.*, 1964, **7**, 625. Amino-substituted penthienoindoles with pharmacological properties are disclosed in US 3142678. 1,2,3,4-Tetrahydro-cyclopent[b]indoles are disclosed in FR 2242983 and DE 2438413. 4-(3-Aminobutyl)-1,2,3,4-tetrahydrocyclopent[b]indole has been described in *Khim. Geterotskikl. Soedin,* 1970, **6**, 371.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for $5\text{-}HT_{2B}$ and/or $5\text{-}HT_{2C}$ receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting $5\text{-}HT_{2C}$ receptor ligands, preferably $5\text{-}HT_{2C}$ receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4, R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

R_5 is selected from halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

A is an optionally substituted 5 or 6-membered unsaturated or saturated ring optionally containing one or more heteroatoms.

Compounds of the present invention include salts and addition compounds of the compounds of formula (I). The present invention also includes prodrugs which are metabolised in vivo to a compound of formula (I).

As used herein, the term "lower alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the lower alkyl group is preferable C_5, C_6 and C_7. Where acyclic, the lower alkyl group is preferably methyl, ethyl, propyl or butyl, more preferably methyl.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl or butyl, more preferably methyl.

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thiophenyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon containing groups such as

alkyl,

aryl,

arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),

ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl)

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters

(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonyloxy, alkycarbonyloxyalkyl)

and amides

(e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

and carbamates

(eg. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or dialkylaminocarbonyloxy, arylaminocarbonyloxy),

and ureas

(eg. mono- or dialkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,
nitriles (e.g. cyano, cyanoalkyl),
nitro;

sulfur containing groups such as
thiols, thioethers, sulfoxides, and sulfones
(e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatoms,
(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen.

The compounds of formula (I) are selected from compounds in which R_3 is lower alkyl, preferably methyl.

R_5 is selected from halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, amino, alkylamino, dialkylamino, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl.

R_4 , R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, amino, alkylamino, dialkylamino, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

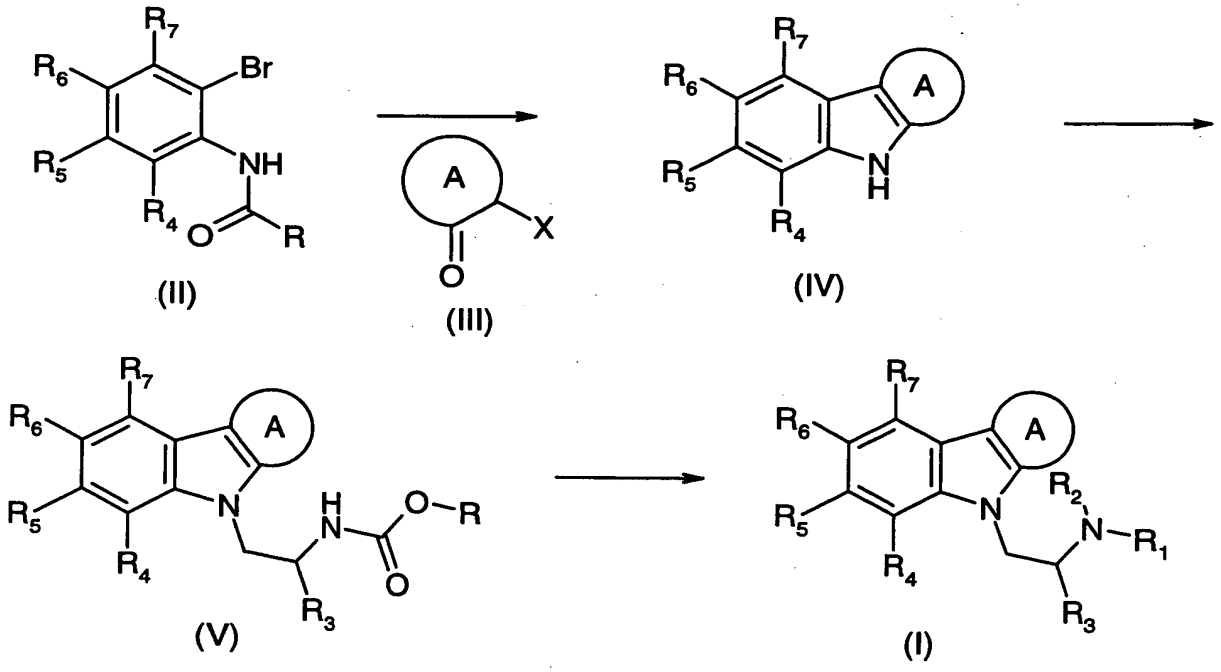
According to a further aspect of the invention, there is provided a method of treating a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I) described below in the Reaction Scheme. R_1 to R_7 are as previously defined.

The saturated 2,3-ring-fused indoles (IV) may be formed by sequential reaction of the suitably substituted N-2-bromophenyl acetamide (eg R = CF_3) (II) with methyllithium and the appropriate 2-halo-cyclic ketone (III), followed by *tert* butyllithium and then trifluoroacetic acid. The N-alkyl ring-fused indole (V) (eg R= *tert* Bu) may then be obtained by reaction of (IV) with an appropriate carbamylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. The indole (I) ($R_1 = R_2 = H$) may then be obtained by reaction of the indole (V) with a reagent suitable to reveal the protected amine function.

Reaction Scheme



The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) ($R_1 = R_2 = H$) by standard methods such as reductive

alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

The unsaturated 2,3-ring-fused indoles (I) may be formed in a similar manner to the saturated 2,3-ring-fused indoles (I), through the intermediacy of the unsaturated 2,3-ring-fused indole (IV) obtained from the saturated 2,3-ring-fused indole (IV) under standard dehyrogenation conditions such as through treatment with DDQ or Pd on carbon in a suitable solvent such as dioxan and xylene respectively.

If, in any of the other processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds. Examples of acid addition salts are those formed from inorganic and organic acids, such as sulfuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulfonic, p-toluenesulfonic, oxalic, hippuric or succinic acids.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilising and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2c} receptor the 5-HT_{2c} receptors were radiolabelled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2c} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabelled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabelled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, **9/10**, 3482-90.

The thus determined activity of the compound of the Example is shown in Table 1.

Table 1

Compound	**Method (a)** K_i **(2C)**	**Method (b)** K_i **(2B)**	**Method (c)** K_i **(2A)**
Example	74	40	122

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR) in the following manner.

CHO cells expressing either the h5-HT_{2C}, h5-HT_{2A} or h5-HT_{2B} receptors were counted and plated into standard 96 well microtitre plates before the day of testing to give a confluent monolayer. The following day the cells were dye loaded with the calcium sensitive dye Fluo 3-AM by incubation with serum free culture maintenance media containing pluronic acid and Fluo 3-AM dissolved in DMSO at 37 °C in a CO_2 incubator at 95% humidity for approximately 90 minutes. Unincorporated dye was removed by washing with Hanks balanced salt solution containing 20mM HEPES and

2.5mM probenecid (the assay buffer) using an automated cell washer to leave a total volume of 100 µL/well.

The drug (dissolved in 50 µL of assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements are taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5 -HT (defined as 100%) to which it is expressed as a percentage response (relative efficacy).Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

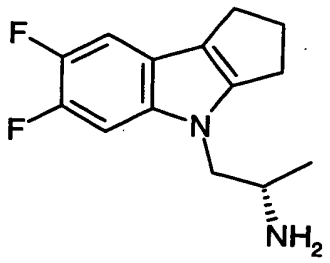
The thus determined activity of the Example is shown in Table 2.

Table 2

Compound	h5-HT_{2C}		h5-HT_{2A}		h5-HT_{2B}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example	272	77	>10000	-	82	85

Synthetic Examples

Example 1: (*S*)-1-(6,7-difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indol-4-yl)-2-propylamine fumarate



2'-Bromo-2,2,2-trifluoroacetanilide

To a stirred solution of 2-bromo-4,5-difluoroaniline [H. Ishikawa, T. Uno, H, Miyamoto, H. Hiraki, H. Tamaoka, M. Tominaga and K. Nakagawa, *Chem. Pharm. Bull.*, 1990, 38(9), 2459-2462] (7.2 g, 34 mmol) in ether (50 mL) at 0 °C was added sodium carbonate (5.4 g, 44 mmol) and trifluoroacetic anhydride (6.2 mL, 44 mmol). The reaction mixture was stirred at room temperature for 1 h. Water (100 mL) was added and the mixture was extracted with dichloromethane (3 x 100 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give the product (9.9 g, 94%) as a white solid. IR ν_{max} (Nujol)/cm^{-1} 3270, 1716, 1550, 1489, 1465, 1226, 1181, 919, 876 and 821; NMR δ_H (400 MHz, $CDCl_3$) 7.45-7.5 (1H, dd, *J* 7.5 Hz), 8.28-8.34 (1H, dd, *J* 8 Hz) and 8.36 (1H, br s).

6,7-Difluoro-8a-hydroxy-1,2,3,3a,4,8a-hexahydrocyclopent[*b*]indole

A stirred solution of 2'-Bromo-2,2,2-trifluoroacetanilide (5.3 g, 35 mmol), in tetrahydrofuran (200 mL) was cooled to –78 °C. A solution of methyllithium (12.5 mL, 35 mmol, 1.4 M in ether) was added maintaining the temperature of reaction below -75 °C. After 10 min a solution of *tert*-butyllithium (20.5 mL, 70 mmol, 1.7 M in pentane) was added over 5 min and the reaction was stirred for 1 h at –78 °C. The mixture was warmed to – 50 °C and 2-chlorocyclopentanone (2.1 mL, 42 mmol) was added dropwise. The reaction was warmed slowly to room temperature and stirred for a further 2 h. A solution of potassium hydroxide in methanol (10%, 20 mL) was added and the mixture was stirred at room temperature for 12 h. The mixture was poured onto dilute hydrochloric acid (5%, 150 mL) and washed with dichloromethane (3 x 150 mL). The aqueous layer was basified (15% aqueous sodium hydroxide solution) and extracted with dichloromethane (3 x 150 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give the product (0.85 g, 11%) as a pale brown solid. R_f 0.39 [SiO_2; heptane-ethyl acetate (10:3)]; NMR δ_H (400 MHz, $CDCl_3$) 1.53-1.67 (2H, m), 1.78-1.89 (1H, m), 2.02-2.17 (2H, m), 2.29-2.37 (1H, m), 4.04 (1H, dd, *J* 6 Hz), 6.21-6.26 (1H, m) and 6.86-6.94 (1H, m).

6,7-Difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indole

A stirred solution of 6,7-difluoro-8a-hydroxy-1,2,3,3a,4,8a-hexahydrocyclopent[*b*]indole (1.1 g, 5.2 mmol), in dichloromethane (150 mL) was cooled to 0 °C. Trifluoroacetic acid (20 drops) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured onto saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3 x 50 mL). The organic extracts were combined, dried (magnesium sulfate), filtered, concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-heptane (1:5)]to give the product (0.78 g, 78%) as a white crystalline solid. IR ν_{max} (Nujol)/cm^{-1} 3467, 2925, 2854, 1565, 1515, 1450, 1348, 1327, 1244, 1053, 1025, 977, 857, 783, 630 and 516; NMR δ_H (400 MHz, $CDCl_3$) 2.49-2.58 (2H, m), 2.79-2.87 (2H, m), 2.9-2.96 (2H, m), 6.81-6.95 (2H, m), and 7.83 (1H, br s).

(*S*)-4-[2-(*tert*-Butoxycarbonylamino)propyl]-6,7-difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indole

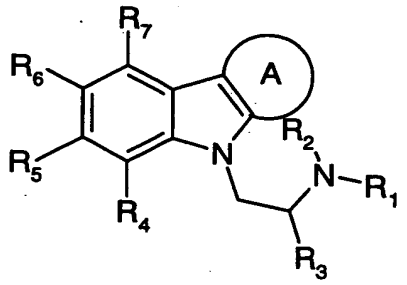
6,7-Difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indole (0.56 g, 2.9 mmol) was added portionwise to a mixture of methyl sulfoxide (15 mL) and crushed potassium hydroxide (0.57 g, 10.2 mmol). The mixture was warmed to 35 °C and stirred for 30 min. A solution of (*S*)-2-(*tert*-butoxycarbonylamino)propane methanesulfonate (1.85 g, 7.3 mmol) in methyl sulfoxide (5 mL) was added over a 1 h period, the mixture was then stirred at 35 °C for 20 h. Water (30 mL) was added and the mixture was extracted with ether (3 x 50 mL). The organic extracts were combined, dried (magnesium sulfate), filtered, concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (5:1)] to give the product (0.55 g, 52%) as a white crystalline solid; IR ν_{max} (Nujol)/cm^{-1} 3366, 1684, 1516, 1456, 1248, 1022 and 773; NMR δ_H (400 MHz, $CDCl_3$) 1.1 (3H, d, *J* 7 Hz), 1.43 (9H, br s), 2.48-2.57 (2H, m), 2.79-2.87 (2H, m), 2.91-2.98 (2H, m), 3.84-3.92 (1H, dd, *J* 7 Hz), 3.96-4.07 (1H, m), 4.08 (1H, br s), 4.4 (1H, br s), 6.83-6.92 (1H, m) and 6.94-7.08 (1H, br s).

(*S*)-1-(6,7-Difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indol-4-yl)-2-propylamine fumarate

A solution of (*S*)-4-[2-(*tert*-butoxycarbonylamino)propyl]-6,7-difluoro-1,2,3,4-tetrahydrocyclopent[*b*]indole (0.4 g, 1.1 mmol) and trifluoroacetic acid (5 mL) in dichloromethane (15 mL) was stirred at room temperature for 1 h. The mixture was made basic by the addition of aqueous sodium hydroxide solution (2 N), then extracted with dichloromethane (3 x 50 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give an orange oil. The oil was dissolved in 2-propanol (5 mL) and the solution was heated to boiling then fumaric acid (0.38 g, 3.3 mmol) was added. The mixture was cooled to room temperature and filtered. The filter-cake was washed (2-propanol, ether) and dried *in vacuo* to give the title compound (0.89 g, 68%) as a pale orange solid. mp. 154-156 °C (dec.); NMR δ_H (400 MHz, DMSO-d_6) 1.13 (3H, d, *J* 7 Hz), 2.43-2.52 (2H, m), 2.78-2.94 (4H, m), 3.5-3.57 (1H, m), 4.13 (1H, d, *J* 8 Hz), 4.29 (1H, dd, *J* 6.5 Hz), 6.55 (2H, s), 7.01-7.10 (1H, m) and 7.26-7.31 (1H, m).

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4, R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

R_5 is selected from halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

A is an optionally substituted 5 or 6-membered unsaturated or saturated ring optionally containing one or more heteroatoms.

2. A compound according to claim 1 wherein R_1 is the same as R_2.

3. A compound according to claim 1 wherein R_1 and R_2 are hydrogen.

4. A compound according to claim 1, 2 or 3 wherein R_3 is lower alkyl.

5. A compound according to claim 1, 2 or 3 wherein R_3 is methyl.

6. A compound according to any of claims 1 to 5 wherein one or more of R_4, R_6 and R_7 is/are hydrogen.

7. A compound of formula (I) as set out in any one of claims 1 to 6 for use in therapy.

8. The use of a compound of formula (I) as set out in any of claims 1 to 6 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

9. A use according to claim 8 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders,

mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

10. A use according to claim 8 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

11. A use according to claim 10 wherein said toxic or infective CNS disease is encephalitis or meningitis.

12. A use according to claim 8 wherein the cardiovascular disorder is thrombosis.

13. A use according to claim 8 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

14. A use according to claim 8 wherein said medicament is for the treatment of obesity.

15. A use according to any one of claims 8 to 14 wherein said treatment is prophylactic treatment.

16. A method of treatment of any of the disorders set out in claims 8 to 13 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 6.

17. A method of treatment according to claim 16 wherein said disorder is obesity.

18. A method according to claim 16 or 17 wherein said treatment is prophylactic treatment.

19. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 6.

20. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 6 in combination with a pharmaceutically acceptable carrier or excipient.

21. A method of making a composition according to claim 20 comprising combining a compound of formula (I) as set out in any one of claims 1 to 6 with a pharmaceutically acceptable carrier or excipient.